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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/725,182 | 11/29/00 | RYAN J | 0207-0007 (W |

HM12/0731
OFFICE OF THE STAFF JUDGE ADVOCATE
U.S. ARMY MEDICAL RESEARCH AND MATERIEL
ATTN: MCMR-JA (MS. ELIZABETH ARWINE)
504 SCOTT STREET
FT. DETRICK MD 21702-5012

| EXAMINER | |
|---|---|
| BASKAR, P | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | 9 |

**DATE MAILED:** 07/31/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

File Copy

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/725,182 | RYAN ET AL. | |
| | Examiner | Art Unit | |
| | Padmavathi v Baskar | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3

MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *9-10 , 21-26,28 and 30-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8,11-20,27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims 1-40 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*
18) ☒ Interview Summary (PTO-413) Paper No(s). *7* .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

### *Priority*

1. This application claims Priority to U.S.Provisional Patent Application No 60/168,300 filed (12/1/1999) under 35 U.S.C. 119(e).

### Information Disclosure Statement

2. Information Disclosure Statement filed on 2/21/01 (Paper # 4) is acknowledged and a signed copy is attached to this Office action.

### *Drawings*

3. The drawings are objected by the draftsperson under 37 C.F.R. 1.84 or 1.152. See PTO-948 for details. Correction of the noted defects can be deferred until the application is allowed by the examiner.

### *Election*

4. Applicant's election without traverse of Group I, claims 1-20, 27 and 29 in Paper No. 6 is acknowledged. Office regrets the oversight made on restriction requirement in Paper NO 5 including claims 9-10 in invention I. However, claims 9-10 are drawn to an immunoassay for detecting antigen in a sample and should have been included in Invention II. Examiner has informed the attorney of record (see Paper No # 7) and obtained the permission. Therefore, claims 9, 10, 21-26, 28 and 30-40 are withdrawn from consideration as drawn to non-elected inventions. Claims 1-8, 11-20, 27 and 29 are under examination.

### *Specification - Informalities*

5. This application is informal in the arrangement of the specification. Applicant attention is directed to MPEP 608.01(a).

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

**Arrangement of Specification**

The following order or arrangement is preferred in framing the specification and, except for the title of the invention, each of the lettered items should be preceded by the headings indicated below.

(a) Title of the Invention.
(b) Cross-References to Related Applications (if any).
(c) Statement as to rights to inventions made under Federally-sponsored research and development (if any).
(d) Background of the Invention.
    1. Field of the Invention
    2. Description of the Prior Art.
(e) Summary of the Invention.
(f) Brief Description of the Drawing.
(g) Description of the Preferred Embodiment(s).
(h) Claim(s).
(I) Abstract of the Disclosure.

This application has not followed the directions or order or arrangement in framing the specification as mentioned above. For example; Claims should begin with "I claim" or "'We claim" or "What is claimed is". Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: In claim 1, "fragment" has no support in the specification.

***Claim Rejections - 35 USC 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for an immunoassay for detecting antibodies in a subject comprising the steps of contacting a sample from the subject with a **Leishmania soluble excretory and secretary antigen** prepared by utilizing a protein free medium and detecting the presence or measuring the amount of an **antibody** in a sample bound to the soluble antigen does not reasonably provide an immunoassay for detecting in a subject comprising the steps of contacting a sample from the subject with **any soluble excretory and secretary antigen** prepared by utilizing a protein free medium and detecting the presence or measuring the amount of antibody **fragment** in the sample bound to the soluble antigen as recited broadly in instant claims.

Instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in In re Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988 ) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

With regard to antibody fragment, in the instant case, other than an immunoassay for detecting the presence of antibodies to Leishmania parasites, it does not provide guidance and direction for an immunoassay for detecting fragments of antibody. There is no guidance how to measure the fragments of antibodies in a sample using this assay. Further, it is noted that antibody fragments are not present in a sample to be detected by Leishmania antigen. Based on experiments with proteolytic enzymes such as papain or trypsin which cleave the immunoglobulin molecule (i.e., antibody) into two Fab ($F(ab)_2$) fragments consisting of light

chain fragment and heavy chain fragment (see chapter 9, page 210, left column; Fundamentals of Immunology; edited by William Paul). This Fab portion of the molecule contains the antigen binding site activity. This type of cleavage (i.e., antibody fragment) does not occur in vivo situations to antibodies (i.e., anti-Leishamania antibodies) present in a sample. Further, It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the immunoglobulin. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus binding of an antigen to an antibody is critical. Therefore, altered antibody (i.e., "fragment ") would bind to the antigen as recited in the claims and requires undue experimentation. Further, one can use antibody or fragments to detect an antigen in a subject but one would not be able to detect antibody fragments in a subject.

The specification provides inadequate direction or guidance regarding how to detect fragments of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Therefore, in view of the inadequate guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue

experimentation in order to practice the claimed invention as it pertains to antibodies/fragments capable of binding to soluble antigens.

With regard to soluble antigens, it is well established in the art of parasite immunology detection of antibodies to Leishmania parasites in patients was performed utilizing soluble antigens from Leishmania promastigotes and detecting the presence of antibodies in an infected individual by an immunoassay. However, detecting exposure to Leishmania parasites in a subject with an unknown soluble antigen require undue experimentation. For example, Martin et al 1998 (Annals of Tropical Medicine and Parasitology 1998, 92 (5) 571-577) disclose an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donavani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensing into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase. Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG was detected (see figure 2). Therefore, an immunoassay as claimed utilizing soluble antigens from unknown source requires further experimentation. Specification provides guidance and direction for an immunoassay for detecting exposure to L.donvani or L.mexicana (see figures) utilizing soluble excretory and secretory antigens from L.donvani ATCC strain 30503 and L.mexicana 50157 (specification pages 11-12 and example 2 for making soluble antigen i.e., excretory or secretory antigen) and detecting the presence of antibody (i.e., IgG or IgM). However, there is no evidence or guidance or directions how use any soluble antigen for detecting Leishmania. Therefore, in view of the inadequate guidance in the specification and in

view of the discussion above one skilled in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to soluble antigens.

The enabling disclosure is clearly not commensurate in scope with these claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Clearly there is lack of guidance directing a skilled artisan to practice the instantly claimed method. Without specific guidance or direction and /or working examples, one of ordinary skill in the art would not be able to reproducibly practice the entire scope of the invention as claimed, without undue experimentation.

***Claim Rejections - 35 USC 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin et al 1998 (Annals of Tropical Medicine and Parasitology 1998, 92 (5) 571-577).

Claims are directed to an immunoassay for detecting exposure to Leishmania parasites in a subject comprising contacting a sample from the subject suspected of having Leishmania with a soluble antigen prepared by utilizing a protein free medium and detecting the presence or measuring the amount of an antibody or fragment thereof in the sample bound to the soluble antigen.

Examiner is viewing the soluble antigens as antigens obtained from culturing the promastigotes of L.donovani in a protein free medium.

Martin et al 1998 (Annals of Tropical Medicine and Parasitology July 1998, 92 (5) 571-577) disclose an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensing into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase. Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG was detected (see figure 2). Since the Office does not have the facilities for examining and comparing applicant's protein free medium comprising D, xylose, hepes buffer, L-glutamate and sodium bicarbonate to the protein free medium of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed protein free medium and the prior art protein free medium. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. The prior art anticipated the claimed invention.

### *Claim Rejections - 35 USC 103*

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al as applied above and further in view of Wirtz et al 1989, Bulletin of the World Health Organization 1989, 67/5, 535-542.

Martin et al 1998 (Annals of Tropical Medicine and Parasitology July 1998, 92 (5) 571-577) teach an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensing into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase. Plates were treated with

substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG was detected (see figure 2). However, the prior art does not teach diluting the sample in blocking buffer.

Wirtz et al teach an immunoassay for detecting circulating antibodies to Plasmodium falciparum. The prior art teaches sera were diluted in blocking buffer containing boiled casein (see page 537, left column, lines 22-23). The use of boiled casein in blocking reduced nonspecific binding (page 538, left column third paragraph). Optimum sensitivity was also achieved using boiled casein –Tween 20 blocking buffer, and by adding a solution of boiled casein to the capture antigen diluent (see page 536, left column, second and third paragraphs). Wirtz et al did not teach using the blocking buffer containing casein to dilute serum samples for detecting antibodies to Leishmania. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the immunoassay as taught by Martin et al by diluting the serum samples in blocking buffer containing boiled casein as taught by Wirtz et al with a reasonable expectation of success because it would have helped to reduce the non-specific binding of antibodies to the antigen and thereby increasing the chances of sensitivity of the assay. An artisan of ordinary skills would have been motivated in applying the applying the teaching of Wirtz et al to Martin et al because Wirtz et al suggests that using boiled casein in blocking buffer reduced nonspecific binding (page 538, left column third paragraph). One of ordinary skill in the art would know how to use different concentrations of boiled casein in blocking buffer by titrating the concentration of boiled casein in blocking buffer for diluting serum samples. The claimed invention is prima facie obvious in view of Martin et al and Wirtz et al absent any convincing evidence to the contrary.

15. Claims 11-20, 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al 1998 (Annals of Tropical Medicine and Parasitology 1998, 92 (5) 571-577) in view of WO 99/56755 and Wirtz et al.

Claims are directed to a kit/diagnostic device for the diagnosis of leishmaniasis in a subject comprising a substrate and a soluble antigen of either L.donovani or L.mexicana prepared by utilizing a protein-free medium packaged together for multiple or single use assays. Examiner views diagnostic device as a kit since it comprises Leishmania soluble antigens and means to detect antibody bound to the soluble antigen.

Martin et al teach an immunoassay (i.e., ELISA) for detecting visceral leishmaniasis (see abstract). Promastigotes of L.donovani were cultured in protein free medium, XOM™. The spent medium was collected and centrifuged. Soluble antigen concentration was adjusted and used for coating the micro titer plates (see page 572, left column, second paragraph under preparation of ELISA plates). Test serum was diluted with PBS and dispensing into the coated wells (i.e., contacting a sample from the subject with the soluble antigen). Plates were washed and treated with goat-antihuman IgG conjugated with horseradish peroxidase (i.e., anti-human IgG conjugate) Plates were treated with substrate and the optical density of the contents of each well was read and levels of Leishmania specific IgG was detected (see figure 2). Martin et al did not teach a kit and the blocking buffer. However, Wirtz et al teach an immunoassay for detecting circulating antibodies to Plasmodium falciparum. The prior art teaches sera were diluted in blocking buffer containing boiled casein (see page 537, left column, lines 22-23). The use of boiled casein in blocking reduced nonspecific binding (page 538, left column third paragraph). Optimum sensitivity was also achieved using boiled casein –Tween 20 blocking buffer, and by adding a solution of boiled casein to the capture antigen diluent (see page 536, left column, second and third paragraphs).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to keep all the ingredients disclosed by the prior art in the form of a compact kit since kits are easy to transport and convenient to work in places (economically under developed countries) with less facilities. An artisan of ordinary skill would have been motivated in applying the art disclosed by Martin et al because kits would help in diagnosing leishmaniasis conveniently and do not require trained technical support since it comes with instructions to use. Although Martin et al did not teach that the samples are diluted in blocking buffer, it was well known in the art of immunology as evidenced by Wirtz et al (see Bulletin of the World Health Organization 1989, 67/5, 535-542) that diluting the sample in blocking buffer reduces the nonspecific binding of antibodies to antigens. Kits were well known in the art for testing or diagnosing varieties of parasitic diseases including the one disclosed by the prior art (WO 99/56755, claim 24). The instructions of the kit were also known as taught by WO 99/56755, claim 24. Moreover, instructions are printed matter which have been long been held to distinguish a claimed structure over the prior art only where the printed matter functions in cooperation with the structure. Here there is no such functional cooperation between the printed instructions and the kit's structural components.

The claimed invention is prima facie obvious in view of Martin et al , Wirtz et al and WO 99/56755 absent any convincing evidence to the contrary.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Badaro et al 1986 (Am.J.Trop.Med.Hyg 35 (1) 72-78); Senaldi et al 1996, Journal of Immunological Methods (193; 9-15).

Badaro et al 1986 (Am.J.Trop.Med.Hyg 35 (1) 72-78) disclose an immunoassay (i.e., ELISA) for detecting leishmaniasis using soluble antigen prepared in a protein free medium (see Materials and methods and Table 1).

Senaldi et al disclose an immunoassay (i.e., dot-enzyme immunoassay, see page 11, 2.2 –2.4) for diagnosing leishmaniasis (see abstract) comprising contacting sera (i.e., sera containing exo antigen) from the subject to with a mouse anti-L.donovani monoclonal antibody which is present on nitrocellulose rectangles strips (i.e., substrate).

***Status of Claims***

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.
7/30/01

Padma Baskar 7/30/01